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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,755	11/28/2000	Hans-Michael Wenz	7414.0020-03	8421

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FINNEGAN, HENDERSON, FARABOW, GARRETT &
DUNNER LLP
1300 I STREET, NW
WASHINGTON, DC 20006

EXAMINER

FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
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1637

DATE MAILED: 09/11/2002

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/724,755	WENZ, HANS-MICHAEL
Examiner	Art Unit	
Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM
 THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 22 July 2002.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 52-86 and 115-129 is/are pending in the application.
 - 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 52-86 and 115-129 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 - a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____.
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>12</u> .	6) <input type="checkbox"/> Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 22, 2002 has been entered.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
- (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

2. Claims 52-64, 69-80, 85, 86 and 115-117 are rejected under 35 U.S.C. 102(b) as being anticipated by Barany et al (WO 97/31256).

Barany teaches a kit (page 88, claim 138) comprising

- (a) a plurality of oligonucleotide probe sets wherein each probe set has a different target sequence (page 12, lines 10-34) and comprises
 - (i) a first probe with a target specific portion and a addressable array specific portion, where the 5' terminal nucleotides of the addressable array portion can inherently function as a 5' primer specific portion and
 - (ii) a second probe comprising a target specific portion and a 3' addressable , where the terminal nucleotides of the addressable array portion can inherently function as a primer specific portion,wherein the oligonucleotides in the set are suitable for ligation together when hybridized to each other adjacent to one another on a complementary target sequence
- (b) and where one of the oligonucleotides has a detectable reporter label (page 88, claim 138)
- (c) and a solid support with capture oligonucleotides complementary to the addressable array specific portions,
- (d) and a thermostable ligase such as Tth ligase (page 88, claim 138 and claim 143).
- (e) and a thermostable polymerase such as Taq polymerase (page 15, line 24 and page 89, claim 144).

Barany further teaches the use of fluorescent labels (page 25, lines 9-14) as well as the use of phosphorothioate nucleotides (page 14, lines 12-20 and page 13, lines 35-38). The examiner notes that one embodiment of the Barany kit would involve the entire probe being composed of phosphorothioates (see page 13, lines 35-38 and page 14, lines 12-20).

Barany teaches that the full length capture probe is attached to the solid support at the 5' end by a 5' amino modification which capture probes can inherently also function as primers for amplification (page 52, lines 9-11 and page 36, lines 14-20).

With regard to the orientation of the primer region and addressable region, it is noted that in an oligonucleotide, these terms represent intended use limitations and do not structurally effect the oligonucleotide. That is, for example, the following oligonucleotide:

5' – ACGTACGTGGTGGTGGTGGTAACAACAAACACAC – 3'

is structurally identical, that is exactly the same, irrespective of whether the oligonucleotide has the INTENDED properties in a METHOD as below:

5' – ACGTACGT	GGTGGTGGTGGT	AACAACAAACAC
Addressable region	primer region	target specific region

Or if the oligonucleotide has the INTENDED properties in a METHOD as below:

5' – ACGTACGT	GGTGGTGGTGGT	AACAACAAACAC
primer region	addressable region	target specific region

Or even if the oligonucleotide has the INTENDED properties in a METHOD as below:

5' – ACGTACGTGGTGGTGGTGGT	AACAACAAACAC
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addressable region

target specific region

The ultimate sequence of this oligonucleotide will still be

5' – ACGTACGTGGTGGTGGTGGTAACAAACAAACACAC – 3' in each of the three situations above. Further, any region of any oligonucleotide is inherently and necessarily capable of function as a primer target region, or as an addressable region or as a target specific region, which specificity is solely dependent upon experimental selection of the appropriate primer, capture probe or target.

3. Claims 52-63, 69-79, 85, 86, 115-117 and 120-129 are rejected under 35 U.S.C. 102 (a) and (e) as being anticipated by Barany et al (U.S. Patent 6,027,889).

Barany teaches the use of kits (column 49, line 41) and teaches methods using products comprising

(a) a plurality of oligonucleotide probe sets (column 23, lines 20-33) wherein each probe set has a different target sequence (column 23, lines 20-33 and column 26, line 37 to column 27, line 19) and comprises

(i) a first probe with a target specific portion and a addressable array specific portion, where there is an addressable array portion function and a region which functions as a primer specific portion and

(ii) a second probe comprising a target specific portion and a 3' addressable , where there is an addressable array portion function and a region which functions as a primer specific portion (column 23, lines 20-33 and column 26, line 37 to column 27, line 19),,

wherein the oligonucleotides in the set are suitable for ligation together when hybridized to each other adjacent to one another on a complementary target sequence (column 23, lines 34-53)

- (b) and the use of primers which amplify a primer specific portion of the oligonucleotides (column 23, lines 54-63),
- (c) and where one of the oligonucleotides has a detectable reporter label (column 23, line 60) ,
- (d) and a solid support with capture oligonucleotides complementary to the addressable array specific portions (column 27, lines 10-19),
- (e) and a thermostable ligase such as Tth ligase (column 33, lines 52-67) ,
- (f) and a thermostable polymerase such as Taq (see figure 9, for example).

Barany further teaches the use of fluorescent labels (column 3, lines 28-30).

With regard to the orientation of the primer region and addressable region, it is noted that in an oligonucleotide, these terms represent intended use limitations and do not structurally effect the oligonucleotide. That is, for example, the following oligonucleotide:

5' – ACGTACGTGGTGGTGGTAACAACAAACACAC – 3'

is structurally identical, that is exactly the same, irrespective of whether the oligonucleotide has the INTENDED properties in a METHOD as below:

5' – ACGTACGT	GGTGGTGGTGGT	AACAAACAAACAC
Addressable region	primer region	target specific region

Or if the oligonucleotide has the INTENDED properties in a METHOD as below:

5' – ACGTACGT	GGTGGTGGTGGT	AACAACAACAAAC
primer region	addressable region	target specific region

Or even if the oligonucleotide has the INTENDED properties in a METHOD as below:

5' – ACGTACGTGGTGGTGGTGGTGGT	AACAACAACAAAC
addressable region	target specific region

The ultimate sequence of this oligonucleotide will still be

5' – ACGTACGTGGTGGTGGTGGTAACAACAAACAAAC – 3' in each of the three situations above. Further, any region of any oligonucleotide is inherently and necessarily capable of function as a primer target region, or as an addressable region or as a target specific region, which specificity is solely dependent upon experimental selection of the appropriate primer, capture probe or target.

Barany expressly teaches sets of six probes with identical sequences at the 5' end (see column 51, lines 25-29). Barany expressly teaches the use of sets of probes (see column 45, tables 6 and 7).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 52-86 and 115-129 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Barany et al (WO 97/31256) in view of Xu et al (Tetrahedron Lett. (1997) 38(32):5595-5598).

Barany teaches the limitations of claims 52-64, 69-80, 85, 86 and 115-117 as discussed above. Barany further suggests the use of common primers (see page 19, lines 2-3) as well as expressly teaching multiplexing as discussed above.

Barany does not teach the use of tosylated or iodate oligonucleotides for ligation. Xu teaches tosylated and iodate oligonucleotides for ligation (page 5595).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the ligation kit of Barany with the use of iodate oligonucleotides since Xu states "This makes possible several practically useful template directed ligations, including the ligations of ssDNAs, cyclization of ssDNAs and ligation of sticky ended duplexes. These reactions proceed in good yield and without specialized protecting groups or deprotection conditions. The method further obviates the need for ligase enzyme, which is costly on a preparative scale (page 5598)". An ordinary practitioner would have been motivated to substitute the oligonucleotide of Xu into the method of Barany for the express motivation of efficient ligation in good yield without the expense of the ligase enzyme..

6. Claims 52-64, 69-80, 85, 86 and 115-117 and 120-129 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany et al (WO 97/31256) in view of Boyce-Jacino (WO 99/66076).

This rejection (and the 103 rejection following this rejection) is made so that if this case is appealed, and the Board of Patent Appeals and Interferences determines that, contrary to the express teachings of all of the prior art from the original Mullis polymerase chain reaction patent in 1987 onward, it is not inherent in every

oligonucleotide that there is a primer binding site, this 103 rejection expressly teaches this element.

Barany teaches a kit (page 88, claim 138) comprising

- (a) a plurality of oligonucleotide probe sets wherein each probe set has a different target sequence (page 12, lines 10-34) and comprises
 - (i) a first probe with a target specific portion and a addressable array specific portion, where the 5' terminal nucleotides of the addressable array portion can inherently function as a 5' primer specific portion and
 - (ii) a second probe comprising a target specific portion and a 3' addressable , where the terminal nucleotides of the addressable array portion can inherently function as a primer specific portion,
- wherein the oligonucleotides in the set are suitable for ligation together when hybridized to each other adjacent to one another on a complementary target sequence
- (b) and where one of the oligonucleotides has a detectable reporter label (page 88, claim 138)
- (c) and a solid support with capture oligonucleotides complementary to the addressable array specific portions,
- (d) and a thermostable ligase such as Tth ligase (page 88, claim 138 and claim 143).
- (e) and a thermostable polymerase such as Taq polymerase (page 15, line 24 and page 89, claim 144).

Barany further teaches the use of fluorescent labels (page 25, lines 9-14) as well as the use of phosphorothioate nucleotides (page 14, lines 12-20 and page 13, lines 35-38). The examiner notes that one embodiment of the Barany kit would involve the entire probe being composed of phosphorothioates (see page 13, lines 35-38 and page 14, lines 12-20).

Barany teaches that the full length capture probe is attached to the solid support at the 5' end by a 5' amino modification which capture probes can inherently also function as primers for amplification (page 52, lines 9-11 and page 36, lines 14-20).

Boyce-Jacino teaches an embodiments of probes which teaches that the addressable or capture region can be rearranged with the primer to form a primer, capture, target binding arrangement (see pages 13-18). Specifically, Boyce-Jacino states "In another preferred embodiment, the capture moiety comprises a specific sequence complementary to a PCR primer or portion thereof, used to amplify a region of the template strand.(page 16, lines 5-10)."

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the rearranged primer as taught by Boyce-Jacino in the method of Barany in order to permit amplification of the template strand within the primer in a PCR type reaction. An ordinary practitioner would have been motivated to modify the Barany primer to include a primer sequence within the capture moiety in order to permit amplification of the template strand and to permit nested amplification.

7. Claims 52-86 and 115-129 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany et al (WO 97/31256) in view of Boyce-Jacino (WO 99/66076) and further in view of Xu et al (Tetrahedron Lett. (1997) 38(32):5595-5598).

Barany in view of Boyce-Jacino teaches the limitations of claims 52-64, 69-80, 85, 86 and 115-117 and 120-129 as discussed above.

Barany in view of Boyce-Jacino does not teach the use of tosylated or iodate oligonucleotides for ligation.

Xu teaches tosylated and iodate oligonucleotides for ligation (page 5595).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the ligation kit of Barany with the use of iodate oligonucleotides since Xu states "This makes possible several practically useful template directed ligations, including the ligations of ssDNAs, cyclization of ssDNAs and ligation of sticky ended duplexes. These reactions proceed in good yield and without specialized protecting groups or deprotection conditions. The method further obviates the need for ligase enzyme, which is costly on a preparative scale (page 5598)". An ordinary practitioner would have been motivated to substitute the oligonucleotide of Xu into the method of Barany for the express motivation of efficient ligation in good yield without the expense of the ligase enzyme.

Response to Arguments

8. Applicant's arguments filed July 22, 2002 have been fully considered but they are not persuasive.

Applicant extensively argues that Barany does not teach the ordered structure of the primers. The arguments in the previous final rejection are incorporated by solely by name of parts of a structure represent limitations on the structure. As the CAFC recently affirmed in *In re Cruciferous Sprout Litigation*, Fed. Cir., 02-1031, 8/21/02 ,

"It is well settled that a prior art reference may anticipate when the claim limitations not expressly found in that reference are nonetheless inherent in it. See, e.g., Atlas Powder Co. v. IRECO Inc., 190 F.3d 1342, 51 USPQ2d 1943 (Fed. Cir. 1999); Titanium Metals Corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985). "Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates."

MEHL/Biophile Int'l Corp. v. Milgraum, 192 F.3d 1362, 1365, 52 USPQ2d 1303, 1305 (Fed. Cir. 1999) (finding anticipation of a method of hair depilation by an article teaching a method of skin treatment but recognizing the disruption of hair follicles, citing In re King, 801 F.2d 1324, 1326, 231 USPQ 136, 138 (Fed. Cir. 1986)). "Inherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art."

MEHL/Biophile, 192 F.3d at 1365, 52 USPQ2d at 1305-06; Atlas Powder, 190 F.3d at 1347; 51 USPQ2d at 1946-47.

In the current case it is clear that the prior art reference inherently can meet the structure desired by Applicant. As in the *In re Cruciferous Sprout Litigation* case, the applicant has not invented a new kind of oligonucleotide which necessarily has a new structure that is different from prior art structures. Any known oligonucleotide of sufficient length can be reinterpreted to meet the structural limitations of Applicant's claims. This is illustrated in the rejection, where the identical oligonucleotide may properly be composed of regions "Addressable - primer - target specific" or "primer – Addressable – target specific". Thus, the only difference between these embodiments

is the functional language, and no structural difference necessarily results from this functional language as shown by the rejection.

Applicant next argues that It is not clear what elements are being addressed by the limitation that Barany teaches sets of probes. Applicant is directed to new claims 120-129 which Applicant filed and which incorporate these limitations.

Applicant then repeats the arguments directed towards the 103 rejections. These arguments have already been addressed and the arguments remain unpersuasive for the reasons of record.

Conclusion

1. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 163737

September 4, 2002